
In the name of
God

Electrolyte disorders in Malignancies

Hassan Argani

Emeritus Professor of Nephrology

Renal complications in cancer patients

AKI ➔
- Pre-renal
- Renal➔ Tumor Lysis Syndrome
- Post Renal

Hypertension

Glomerulonephritis

Tubulo-interstitial nephritis

Renal vascular disorders: Arterial or venous disorders

Electrolyte and acid–base disorders

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Electrolytes and acid–base disorders

Etiology of Electrolyte Disorders in Malignancies

The same as those seen in the general population

Caused by the cancer itself (ie, paraneoplastic syndromes)

Caused by Anti-cancer treatment

Types of Electrolyte Disorders in Malignancies

- Hyponatremia
- Hypernatremia
- Hypokalemia
- Hyperkalemia
- Hypomagnesemia
- Hypermagnesemia
- Hypophosphatemia
- Hyperphosphatemia
- Hypocalcemia
- Hypercalcemia

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Hyponatremia

- Hyponatremia is the most common electrolyte disorder encountered in patients with malignancy, occurring in up to 47 percent of hospitalized cancer patients.
- Approximately 14 percent of hyponatremia cases seen in hospitalized patients are associated with an underlying malignancy.
- Hyponatremia in these patients is associated with increased hospital length of stay, increased mortality, and poor response to therapy
- Half of these cases occurs in the hospital setting
- Hospital length of stay is nearly doubled in patients with moderate to severe hyponatremia.
- Hyponatremia may affect patient response to therapy.
- Hyponatremia may limit the use of chemotherapeutic options that require extensive hydration.

Etiologies of Hyponatremia in Patients With Cancer

a. Syndrome of inappropriate antidiuretic hormone secretion

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l. Cerebral salt-wasting
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n. Pain and emotional stress
o. Nausea, vomiting
p. Inappropriate intravenous fluids

Etiologies of Hyponatremia in Patients With Cancer

nausea/pain/medications → a. Syndrome of inappropriate antidiuretic hormone secretion

AVP directly stimulate tumor growth factor

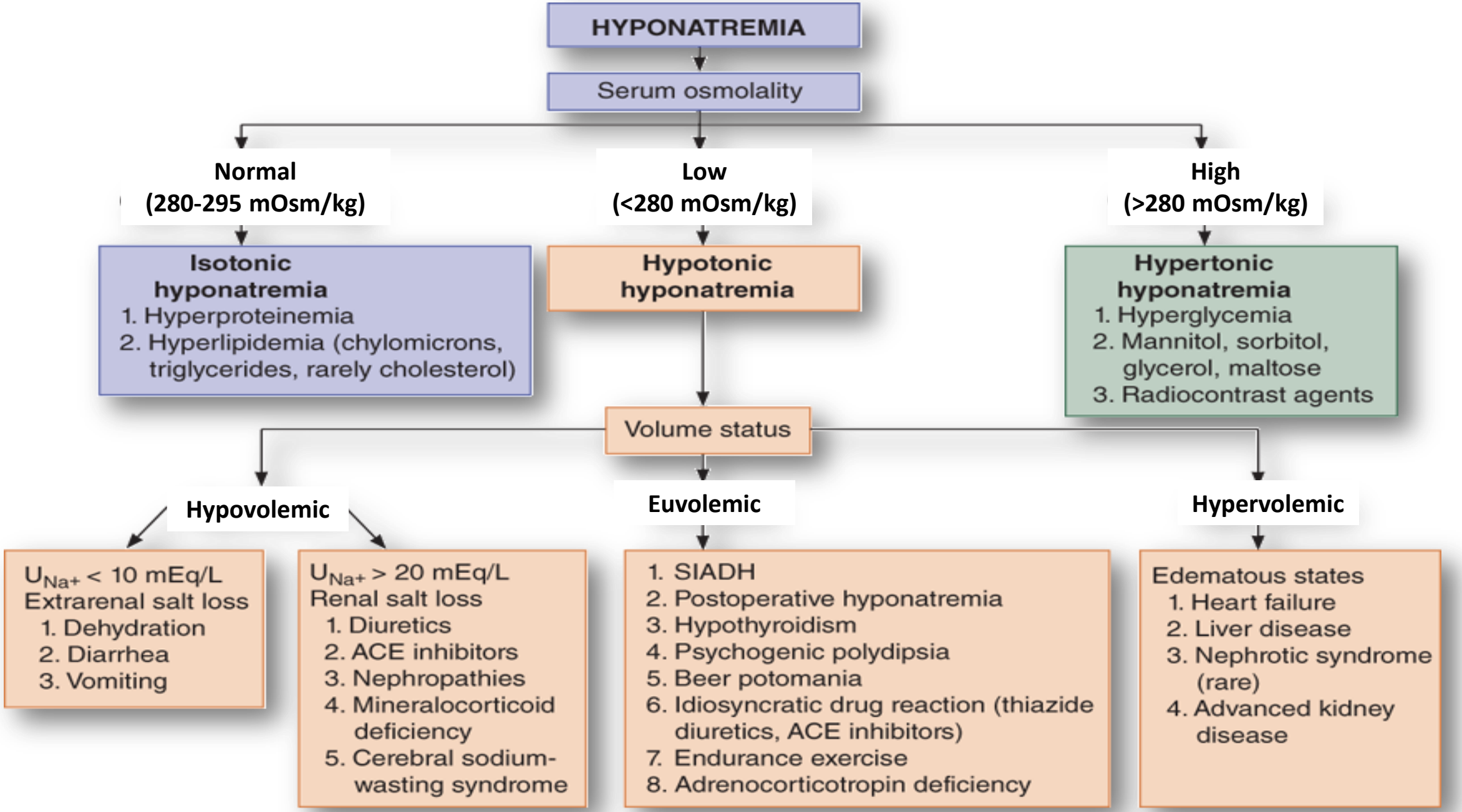
Poor prognosis/poor response to therapy

Malignancies and Therapies Associated With the Syndrome of Inappropriate Antidiuretic Hormone Secretion

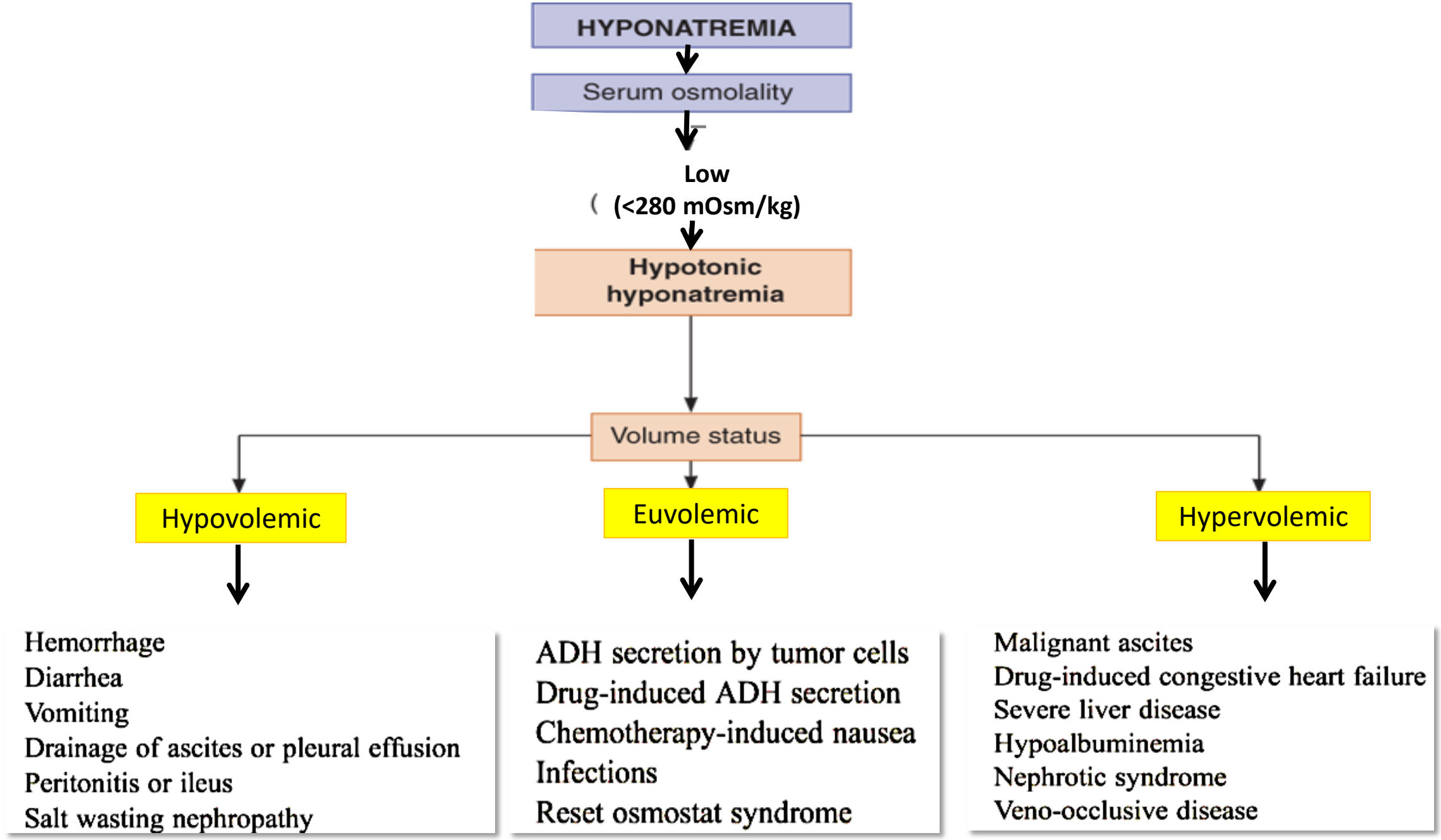
Cancers	Therapies
Small-cell lung cancer	Cyclophosphamide
Head and neck	Hematopoietic stem cell transplantation*
Brain (primary and metastatic)	Bortezomib*
Hematological (lymphoma, leukemia, multiple myeloma)	Vincristine, vinblastine
Skin (melanoma)	Ifosfamide
Gastrointestinal (esophageal, gastric, pancreatic, colon)	Cisplatin, carboplatin
Gynecological	Melphalan*
Breast	Methotrexate*
Prostate	Interferon-α and γ*
Bladder	Levamisole*
Sarcomas	Pentostatin*
Thymoma	Monoclonal antibodies (alemtuzumab, bevacizumab)*
Adrenal	Interleukin-2*
	Busulfan*
	Chlorambucil*
	Cytarabine, fludarabine*
	Hydroxyurea*
	Imatinib*

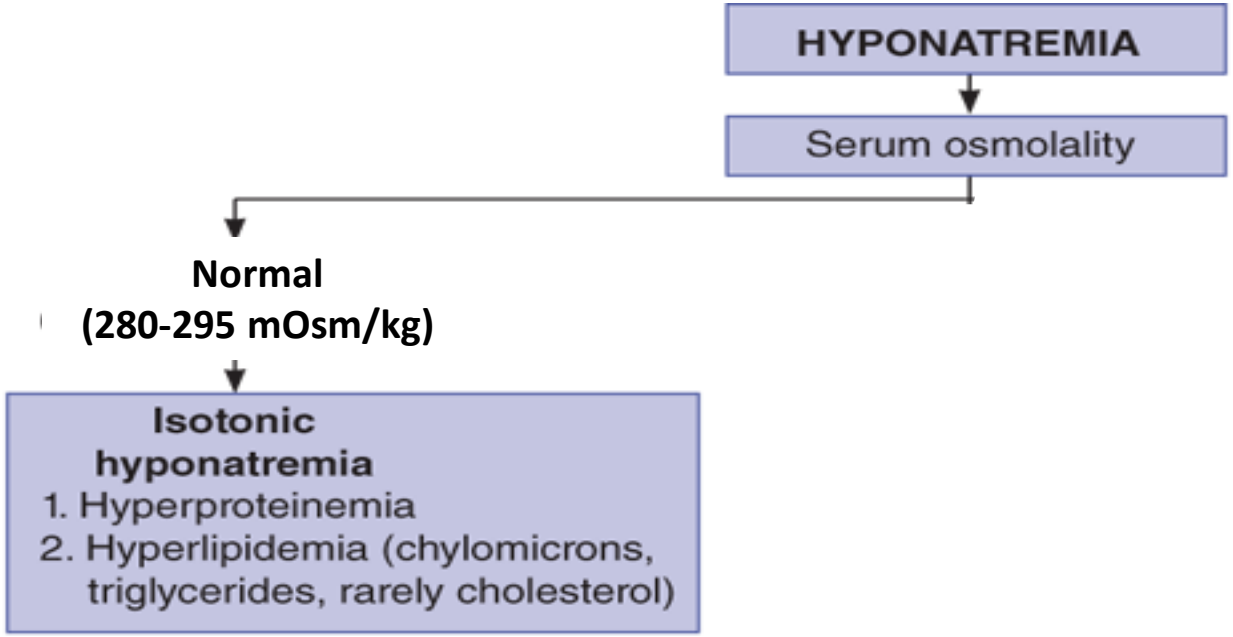
*Mechanism of action is not definitive, but it may involve syndrome of inappropriate antidiuretic hormone secretion.

- ❖ 10% -15% of patients are hyponatremic at presentation.
- ❖ 70% of patients have significant elevations of AVP.
- ❖ Mostly hyponatremia develops slowly and insidiously.



Source: Maxine A. Papadakis, Stephen J. McPhee, Michael W. Rabow: Current Medical Diagnosis & Treatment 2018


HYPONATREMIA
Serum osmolality
Low
(<280 mOsm/kg)
Hypotonic hyponatremia
Volume status
Hypovolemic
Euvolemic
Hypervolemic
Hemorrhage
Diarrhea
Vomiting
Drainage of ascites or pleural effusion
Peritonitis or ileus
Salt wasting nephropathy
ADH secretion by tumor cells
Drug-induced ADH secretion
Chemotherapy-induced nausea
Infections
Reset osmostat syndrome
Malignant ascites
Drug-induced congestive heart failure
Severe liver disease
Hypoalbuminemia
Nephrotic syndrome
Veno-occlusive disease



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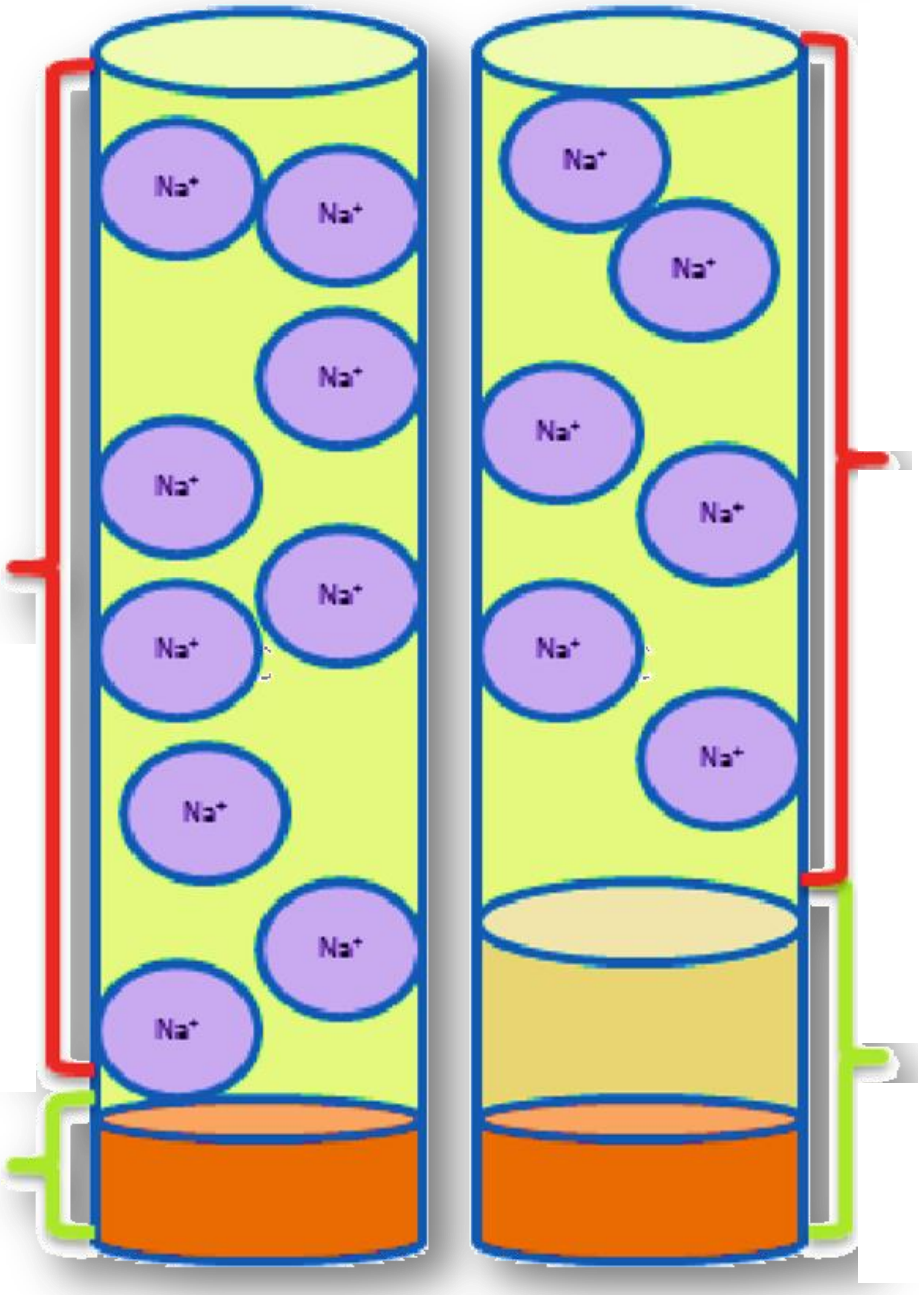
Distribution of water and solids in plasma and electrolyte exclusion effect in the MM

93% Plasma water

Normal Plasma/Serum



Reduced Plasma water

Abnormal Plasma/Serum

7% solid

(Non aqueous phase)

Proteins& Lipids

Increased Solids (Non aqueous phase)

Proteins& Lipids

Original Research Article DOI: 10.18231/2394-6377.2018.0083

Study of dyselectrolytemia in patients with multiple myeloma

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[2]Professor and HOD, [3]Assistant Professor, Dept. of Biochemistry, Father Muller medical College, Mangalore, Karnataka, India

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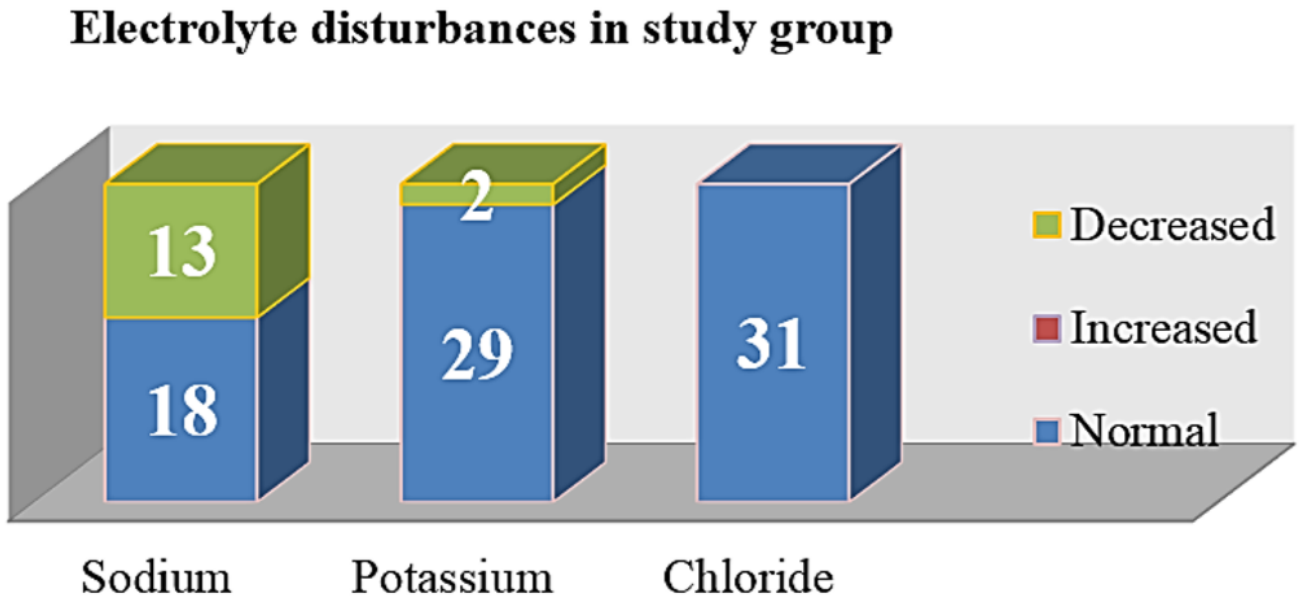
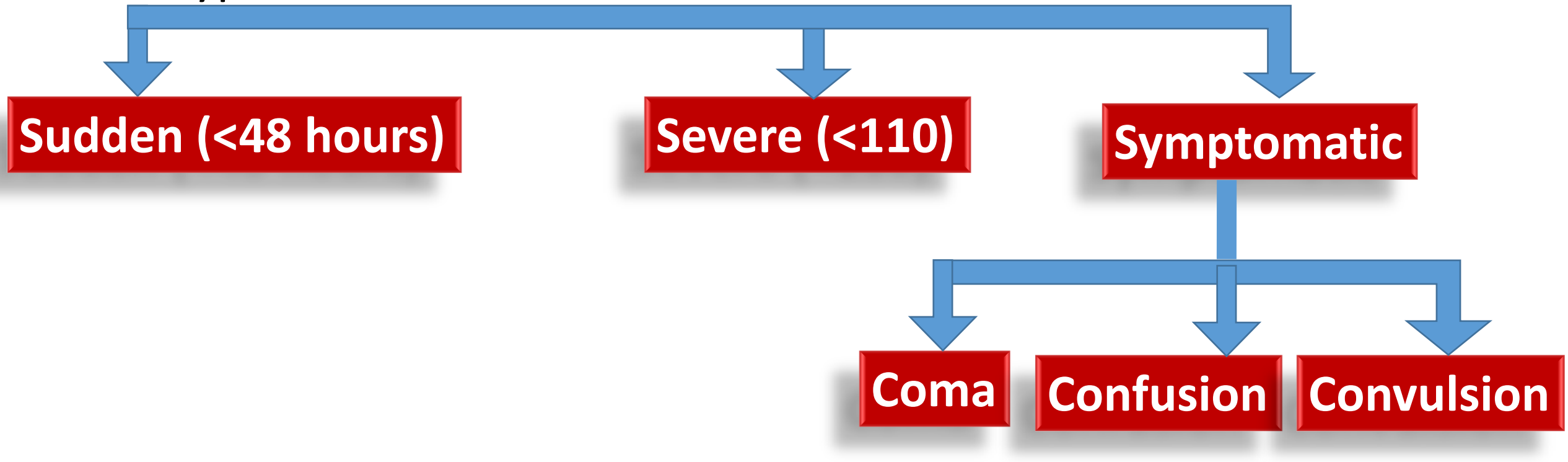


Treatment of malignancy induced hyponatremia

- ❑Treatment of etiology
- ❑Correction of hypoalbuminemia
- ❑Hyponatremia inducible drugs should be minimized
- ❑Fluid restriction (500cc lower than the daily urine volume)
- ❑Hypertonic saline 3%



CEN Case Reports (2019) 8:112–118
https://doi.org/10.1007/s13730-019-00375-7

CASE REPORT

Tolvaptan corrects hyponatremia and relieves the burden of fluid/dietary restriction and hospitalization in hyponatremic patients with terminal lung cancer: a report of two cases

Keiko Kai[1] · Naoto Tominaga[1] · Kenichiro Koitabashi[1] · Daisuke Ichikawa[1] · Yugo Shibagaki[1]

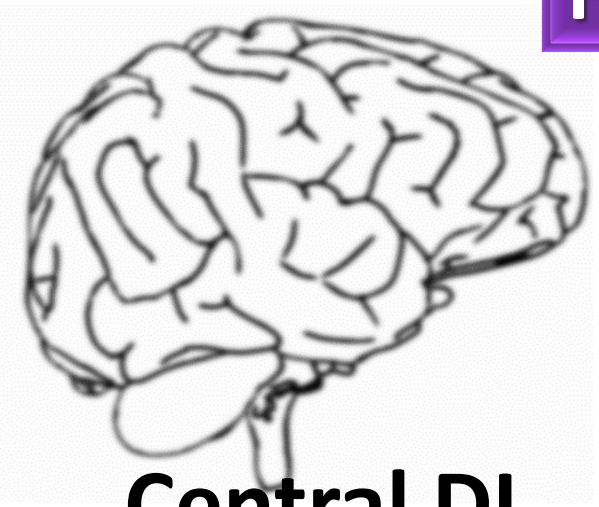
Received: 10 May 2018 / Accepted: 6 January 2019 / Published online: 14 January 2019

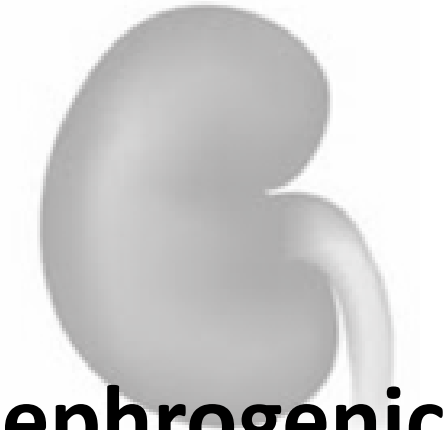
Tolvaptan improves the quality of life of these patients by relieving the burden of strict dietary modifications and prolonged hospitalization

Types of Electrolyte Disorders in Malignancies

- Hyponatremia
- **Hypernatremia**
- Hypokalemia
- Hyperkalemia
- Hypomagnesemia
- Hypermagnesemia
- Hypophosphatemia
- Hyperphosphatemia
- Hypocalcemia
- Hypercalcemia

Hypernatremia in the Malignancies





Central DI

Lung cancer, leukemia, lymphoma, metastasis or neurosurgery for brain tumors.

Nephrogenic DI

Hypercalcemia, or Hypokalemia in patients with cancer

patient does not access to or can not drink water

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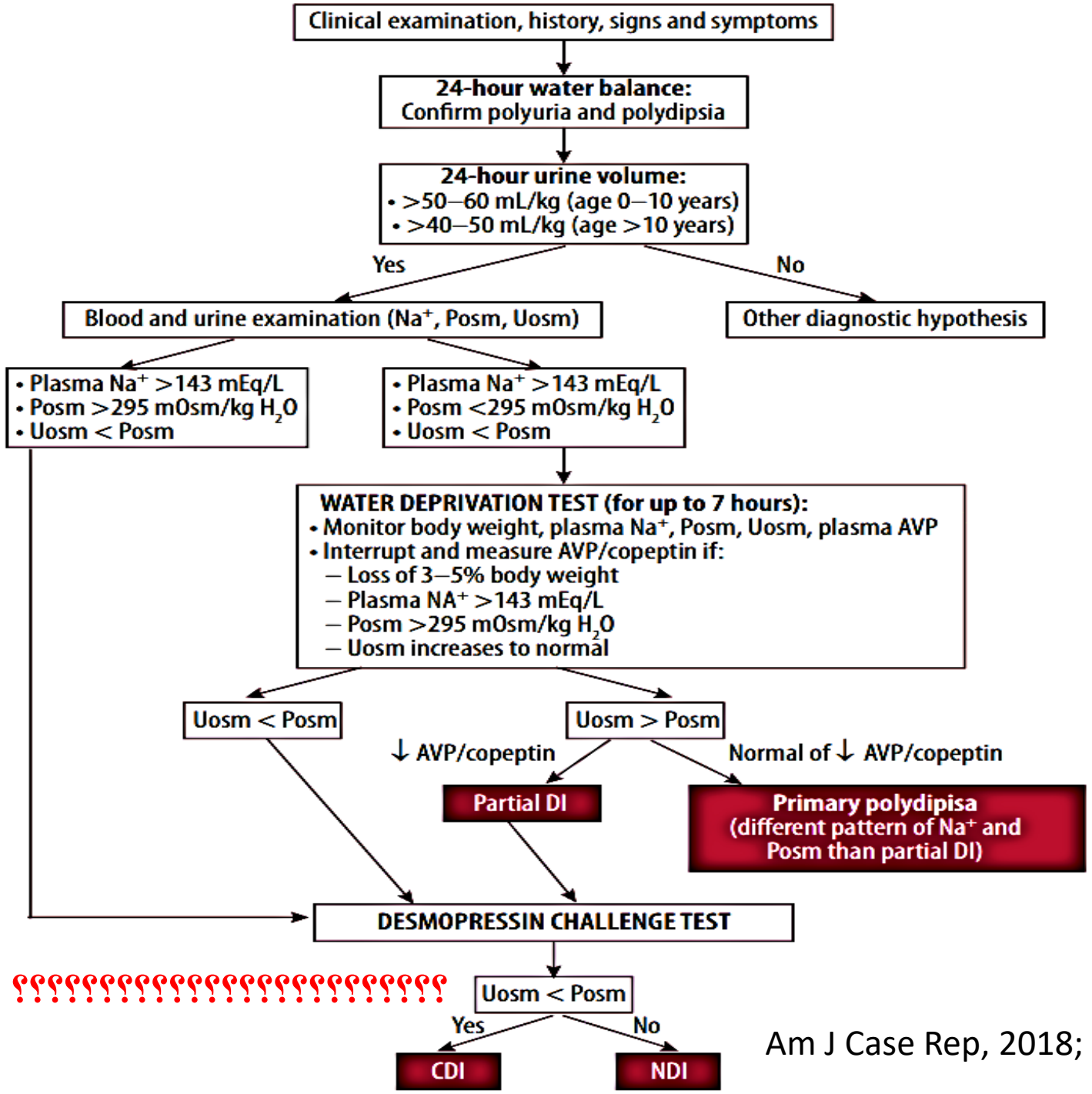
Published: 2018.08.18

Double Trouble – Severe Hypernatremia Secondary to Central Diabetes Insipidus Complicated by Hypercalcemic Nephrogenic Diabetes Insipidus: A Case Report

- A case of 40-year-old female with stage IV breast cancer with skeletal and leptomeningeal metastasis.
- Admitted with polyuria, polydipsia, and recent onset of confusion.
- Found to have profound hypernatremia and severe hypercalcemia.
- Treatment: 5% dextrose for rehydration, 1 dose of intravenous (IV) pamidronate, 1 dose of IV desmopressin, and 4 days of subcutaneous calcitonin 200 international units Q12H.

Diagnosis of DI

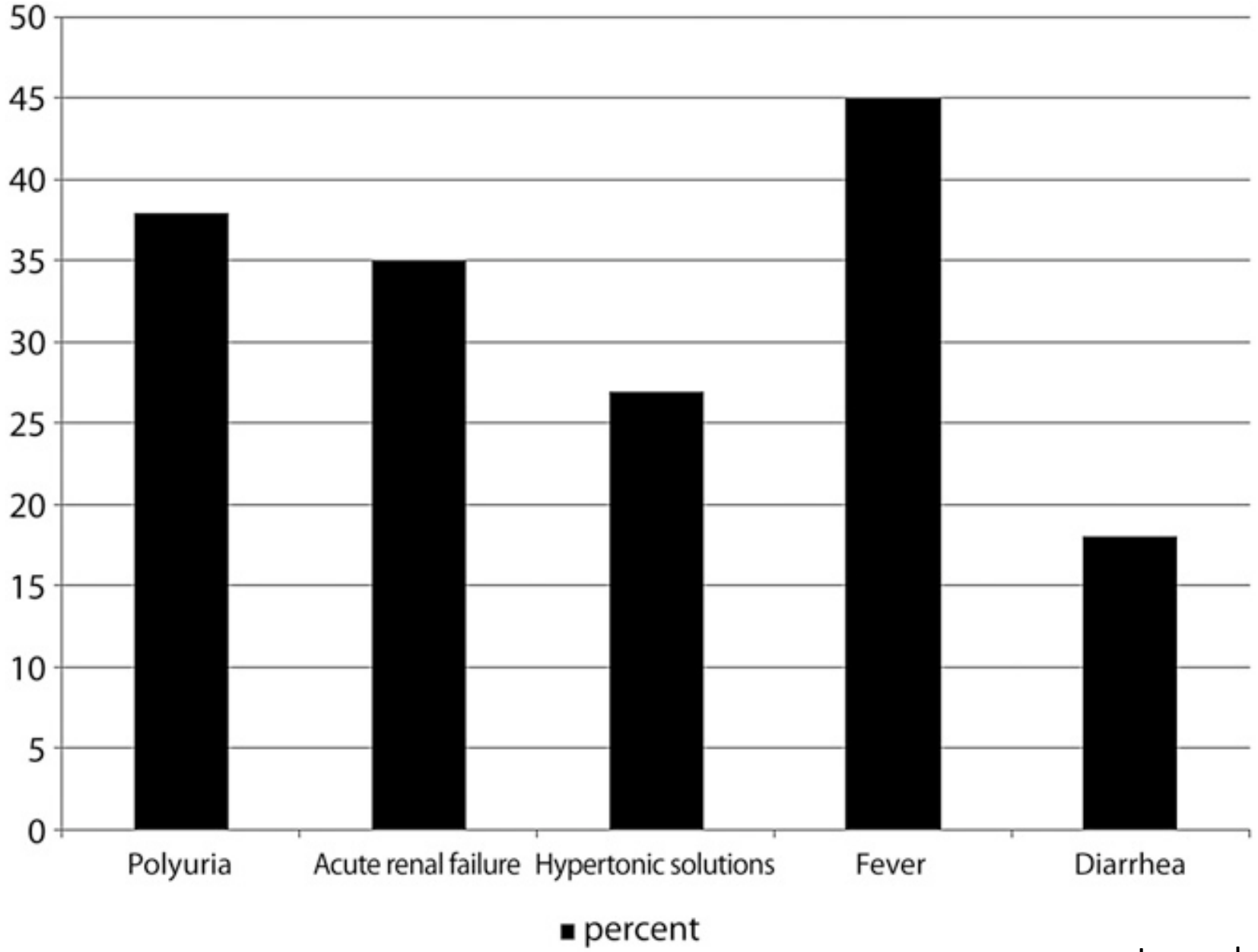


Am J Case Rep, 2018; 19: 973-977

Cancer patients with increased risk for hypernatremia

- Post craniotomy (sellar tumors)
- Elderly, nursing home residents
- Hypertonic infusions
- Tube feedings
- Osmotic diuretics
- Lactulose
- Mechanical ventilation
- Diabetes mellitus with poor glycemic control
- Polyuric disorders

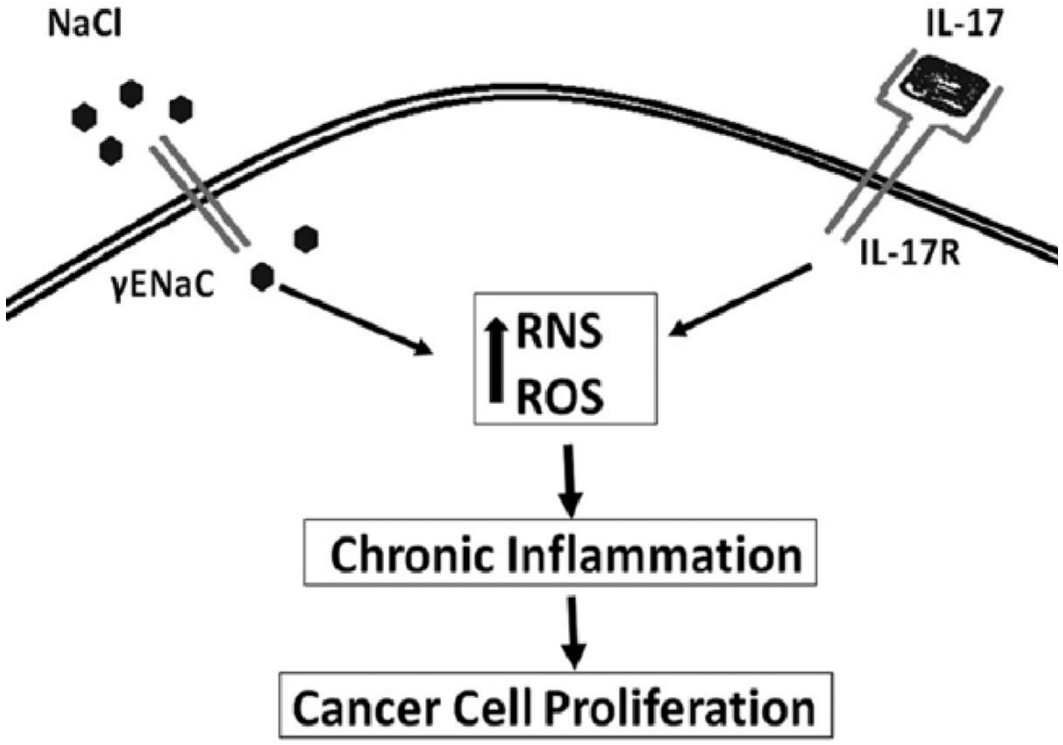
Factors contributing to ICU-acquired hypernatremia (including patients with malignancy)

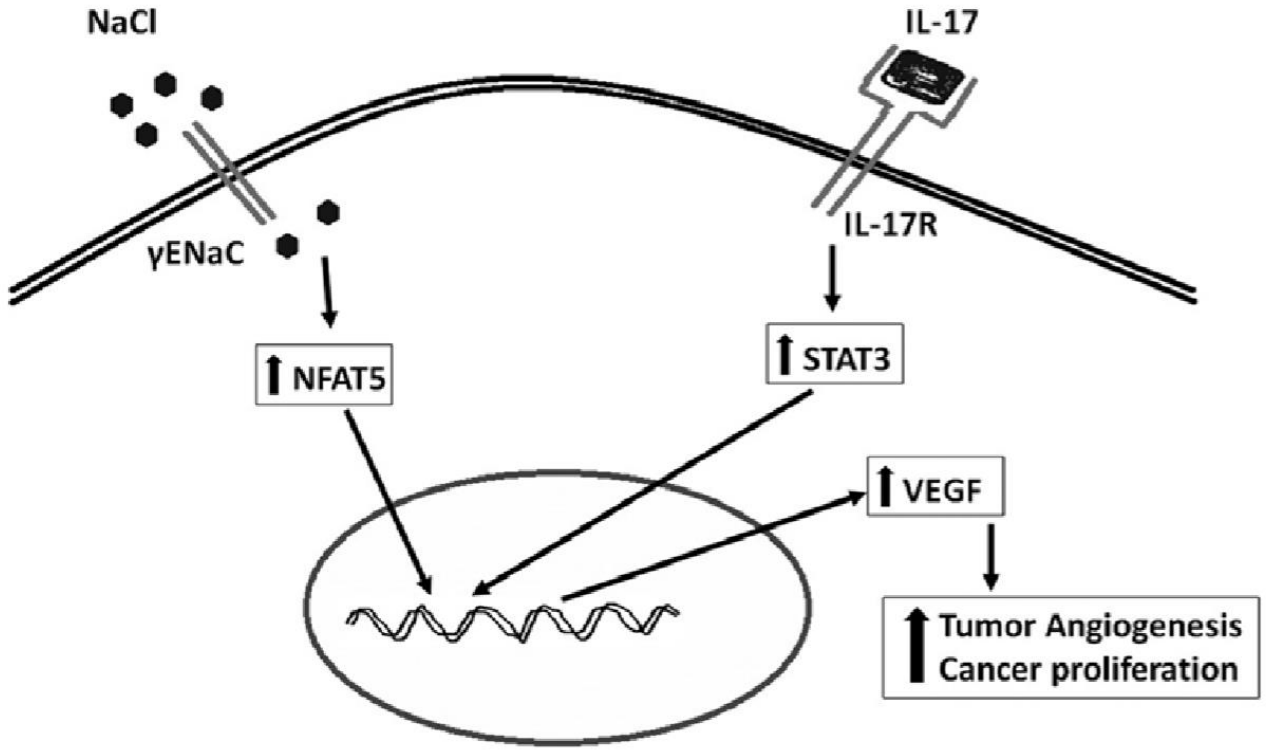


Journal of critical care 2013

Malignancy ⟷ Chronic Inflammation

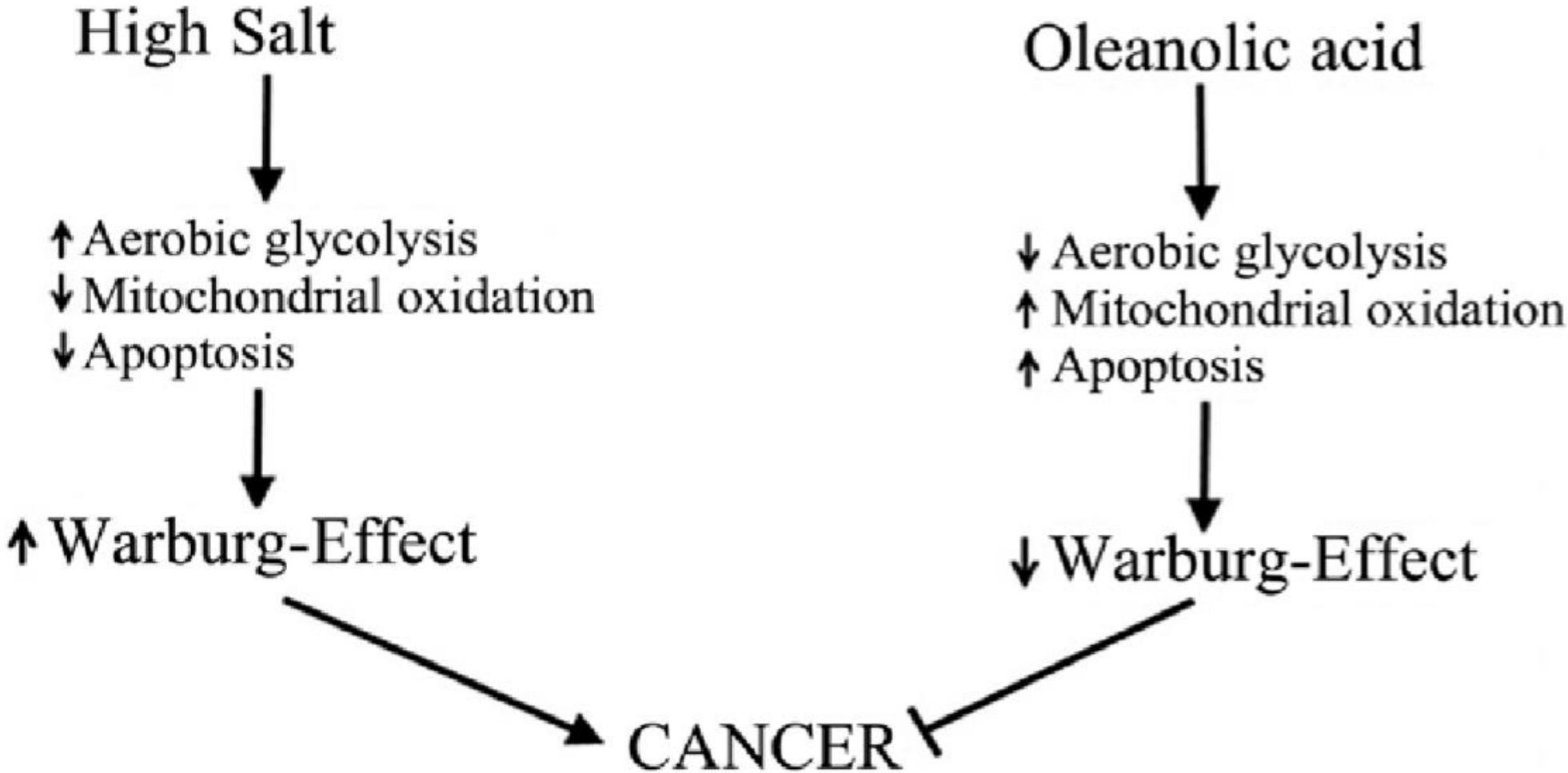
Hypertonic saline ➔ induces Warburg-like effect by enhancing glucose transport and lactic acidosis in cancer cells





INTERNATIONAL JOURNAL OF ONCOLOGY 50: 1477-1481, 2017

Enhanced Warburg-like phenomenon by high salt on cancer cells



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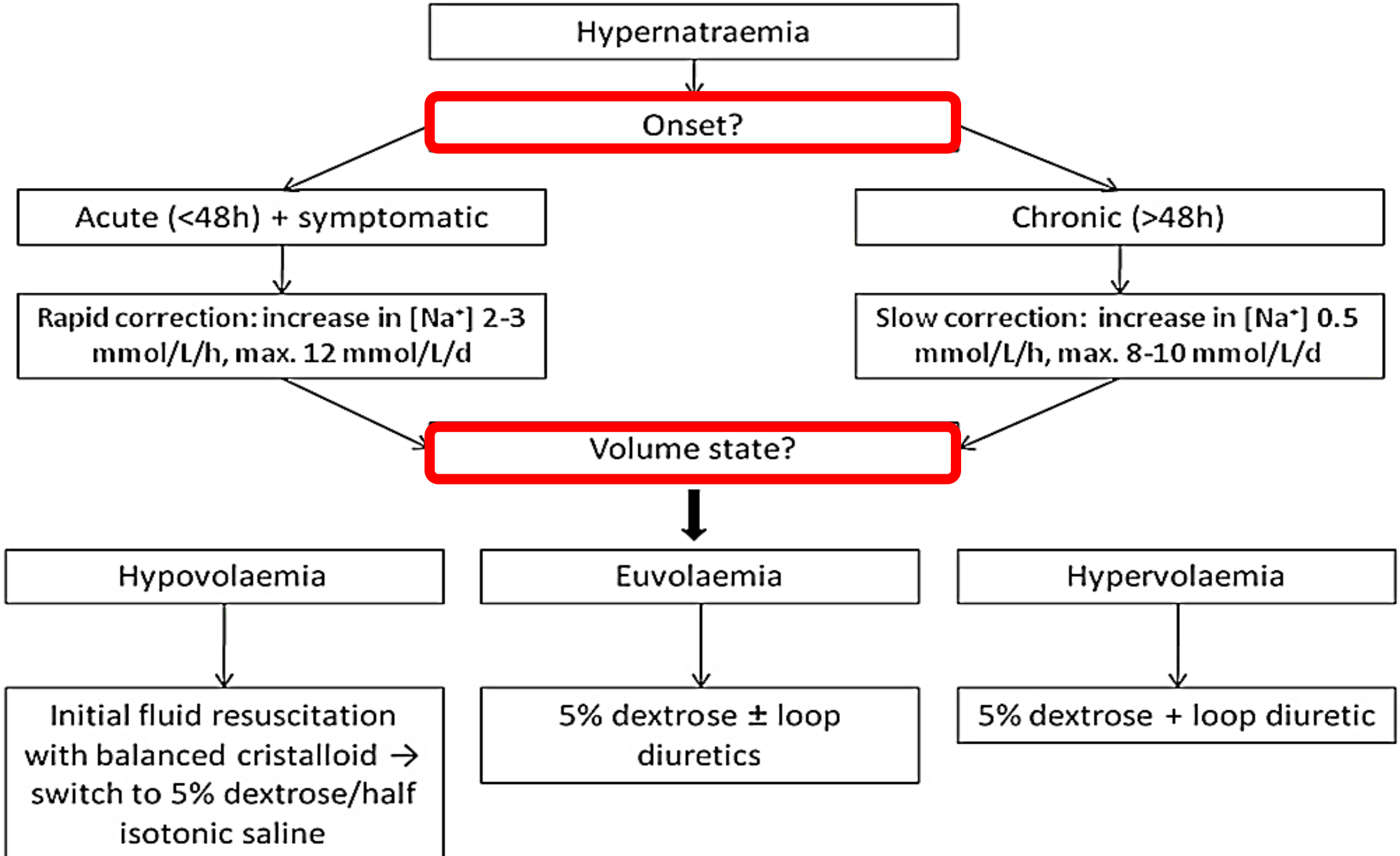
Management of Hypernatremia



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- Hypocalcemia
- Hypercalcemia

Hypokalemia Associated Cancer

- Hypokalemia is the second most common electrolyte disorder encountered in the patient with cancer.
- In most cases, the etiology of hypokalemia is multifactorial.
- Hypokalemia is also commonly seen in conjunction with other electrolyte disorders such as hyponatremia and hypomagnesemia.

Etiologies of Hypokalemia in the Patient With Cancer

- Inadequate potassium intake
- Poor nutrition, anorexia
- Excessive gastrointestinal losses
- Vomiting (chemotherapy-induced)
- Diarrhea (chemotherapy-induced, tumor-associated, postsurgical resection)
- Posturetosigmoid diversion
- Kidney losses- Diuretics
- Hypercalcemia
- Hypomagnesemia
- Postobstructive diuresis
- Drugs
  - Amphotericin B
  - Aminoglycosides
  - Cisplatin
  - Ifosfamide
  - Glucocorticoids
- Lysozymuria with acute leukemia
- Mineralocorticoid excess
  - Primary hyperaldosteronism (adrenal adenoma or carcinoma)
  - Renin-producing tumors
  - Ectopic adenocorticotropin syndrome
- Intracellular shifts
- Pseudohypokalemia
- Use of growth factors and vitamin B12 therapy

May be persistent months to years after the end of treatment

- Directly via renal tubular effects
- Indirectly via side effects of decreased appetite/ intake, vomiting, and diarrhea

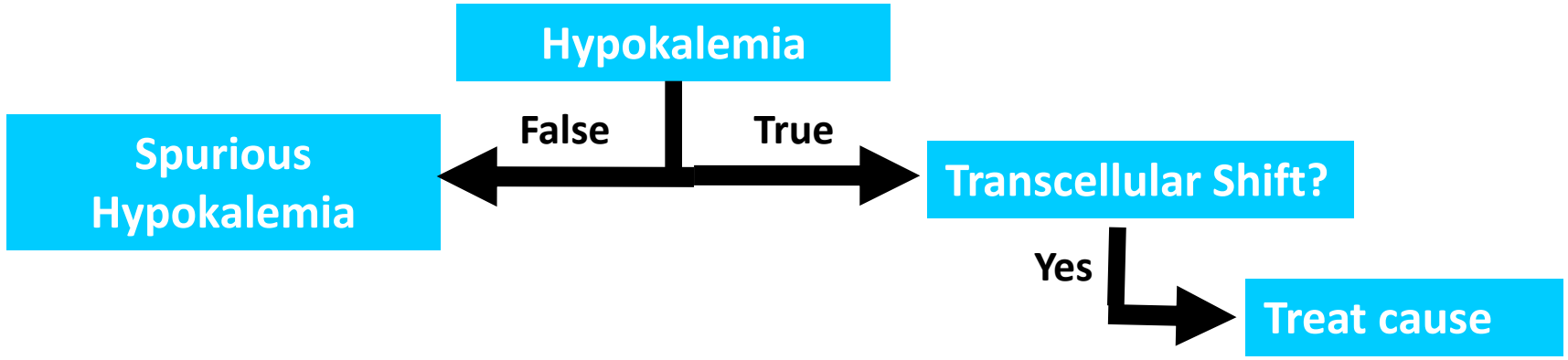
- Up to 50% of AML (type4, 5) developing significant hypokalemia.
- Hypokalemia in these patients is usually associated with other electrolyte disorders (hyponatremia, hypocalcemia, hypophosphatemia, hypomagnesemia.

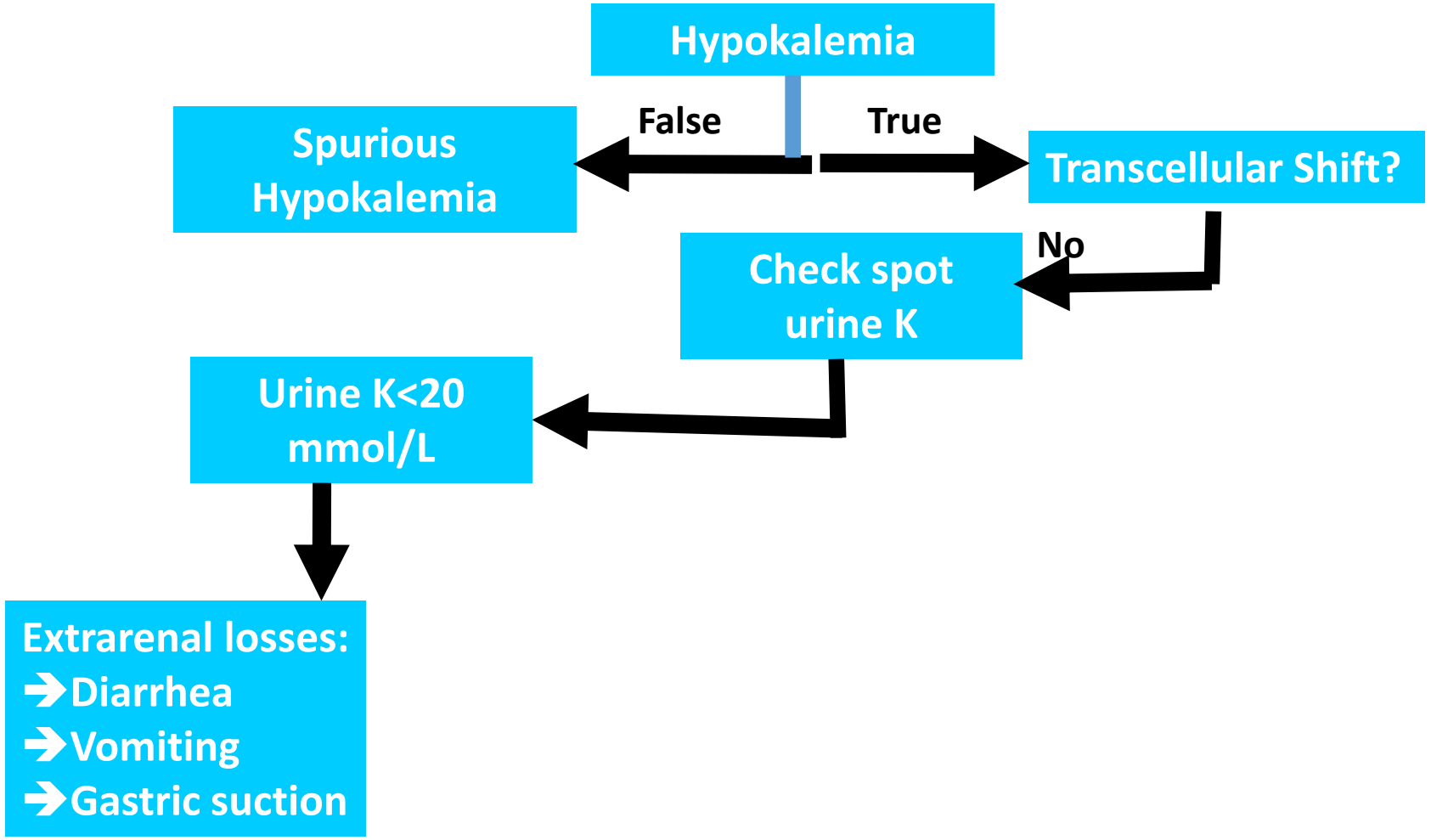
→ Small cell ca, Thymoma, Carcinoid tumors, Thyroid medullary ca, Neuroendocrine tumors

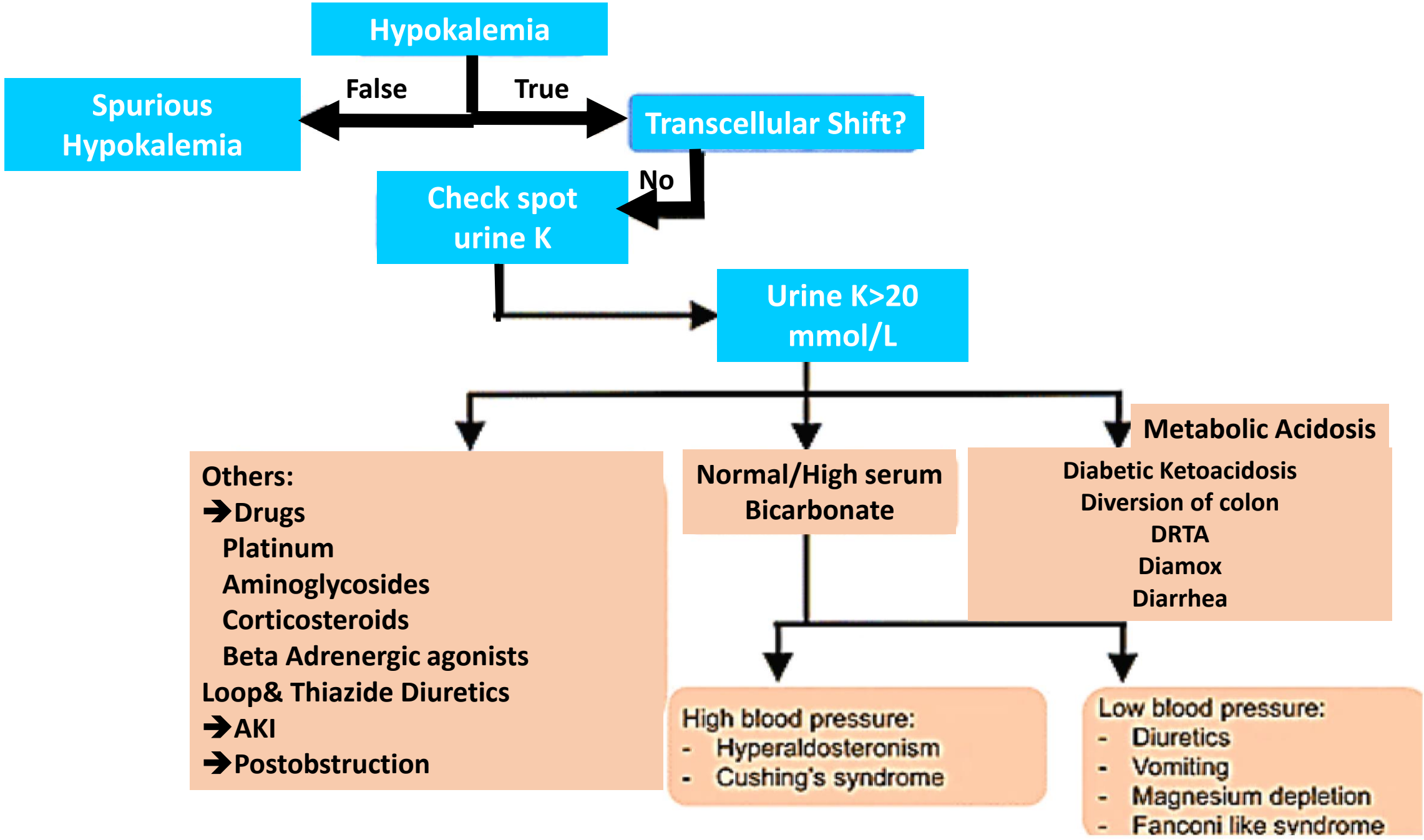
→ Patients with occult ectopic ACTH secretion need adrenalectomy

Rapid separation of the plasma and storage at 4_0C limits this issue

Shift of K into the cells


Hypokalemia
False
True
Spurious Hypokalemia
Transcellular Shift?
Yes
Treat cause


Hypokalemia
False
True
Spurious Hypokalemia
Transcellular Shift?
No
Check spot urine K
Urine K<20 mmol/L
Extrarenal losses:
➔Diarrhea
➔Vomiting
➔Gastric suction


Hypokalemia
False
True
Spurious Hypokalemia
Transcellular Shift?
No
Check spot urine K
Urine K>20 mmol/L
Others:
➔Drugs
Platinum
Aminoglycosides
Corticosteroids
Beta Adrenergic agonists
Loop& Thiazide Diuretics
➔AKI
➔Postobstruction
Normal/High serum Bicarbonate
Metabolic Acidosis
Diabetic Ketoacidosis
Diversion of colon
DRTA
Diamox
Diarrhea
High blood pressure:
- Hyperaldosteronism
- Cushing's syndrome
Low blood pressure:
- Diuretics
- Vomiting
- Magnesium depletion
- Fanconi like syndrome

Treatment for hypokalemia in patients with malignancy

Similar to the patients without an underlying malignancy

- Replacement of potassium deficit
- Treatment of underlying cause
- Treatment of co-associated electrolyte imbalance

Types of Electrolyte Disorders in Malignancies

Hyponatremia

Hypernatremia

Hypokalemia

Hyperkalemia

Hypomagnesemia

Hypermagnesemia

Hypophosphatemia

Hyperphosphatemia

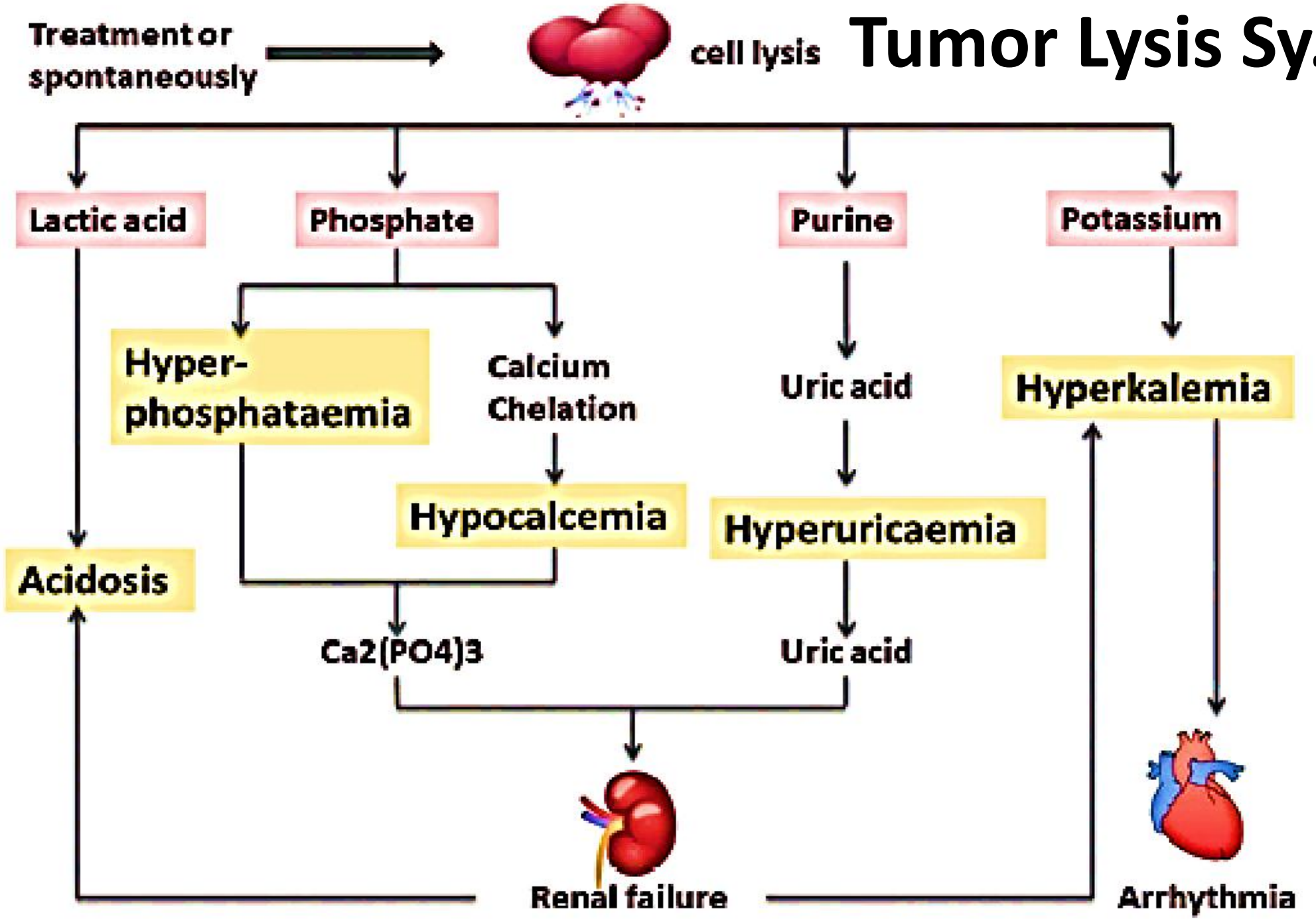
Hypocalcemia

Hypercalcemia

Causes of Hyperkalemia Associated Cancer

- ❑AKI
- ❑Rhabdomyolysis
- ❑Tumor lysis syndrome
- ❑Adrenal insufficiency associated with metastatic disease
- ❑Drugs such as ketoconazole, metapyrone, calcineurin inhibitors (stem cell transplant patients), nonsteroidal anti-inflammatory agents, trimethoprim, and heparin
- ❑Pseudo hyperkalemia, usually in the setting of marked leukocytosis or thrombocytosis. **A serum-to-plasma potassium gradient greater than 0.4 mEq/L is diagnostic of pseudohyperkalemia.**

Tumor Lysis Sy.



Therapy of malignancy induced hyperkalemia

The same as for other non malignant patients

❖**Emergent treatment**

Cardiac protection

Potassium excretion by GI or Urine

❖**Maintenance treatment**

Prohibition of serum potassium accumulation

Types of Electrolyte Disorders in Malignancies

Hyponatremia

Hypernatremia

Hypokalemia

Hyperkalemia

Hypomagnesemia

Hypermagnesemia

Hypophosphatemia

Hyperphosphatemia

Hypocalcemia

Hypercalcemia

Etiology of Hypomagnesemia in the cancer patient

❖Decreased intake

➔Direct effect of Tumor

➔Secondary to the drugs

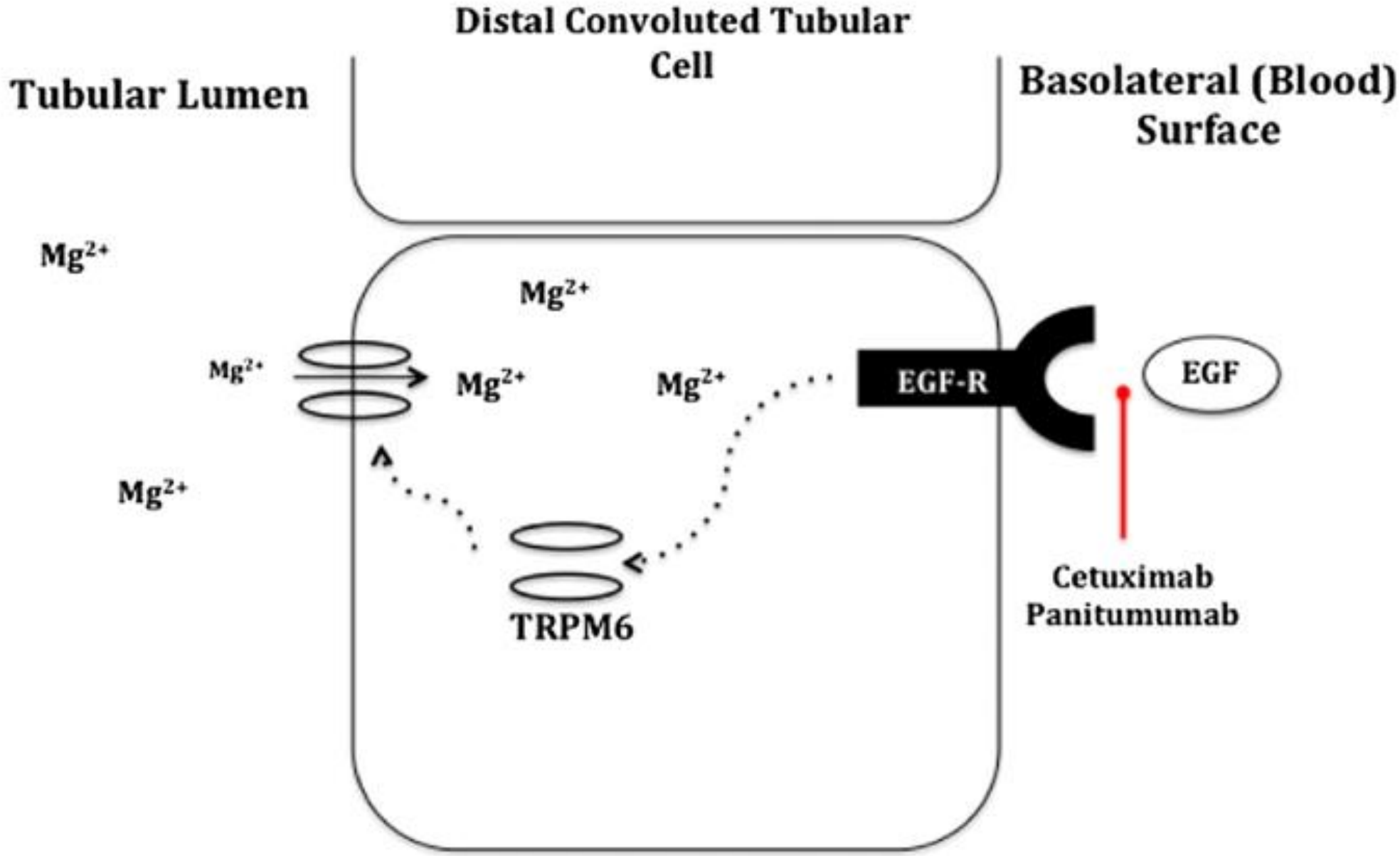
❖Renal magnesium wasting

➔Direct effect of Tumor

➔Secondary to the drugs

A fractional excretion of magnesium>15% in a hypomagnesemic patient indicates renal wasting of Mg

Absorption of magnesium from the tubular lumen is via an EGFR-dependent apical channel, TRPM6



Treatment of malignancy induced hypomagnesemia

- Replacing magnesium as intravenous rout (Diarrhea is a dose-limiting adverse effect of oral magnesium)
- Stop excretion of Mg

Types of Electrolyte Disorders in Malignancies

Hyponatremia

Hypernatremia

Hypokalemia

Hyperkalemia

Hypomagnesemia

Hypermagnesemia

Hypophosphatemia

Hyperphosphatemia

Hypocalcemia

Hypercalcemia

Causes of malignancy induced hypermagnesemia

- Enema with magnesium (for reliving of constipation)
- Renal failure (secondary to Drugs)
- Severe hyperparathyroidism (Parathyroid malignancy)
- Adrenal insufficiency (in the cases of metastasis to the adrenals or sudden corton withdrawal)

Treatment of severe hypermagnesemia

- ❑Cessation of drugs containing Mg
- ❑Rehydration with serum in the abcense of renal failure
- ❑Furosemide
- ❑Calcium gluconate in the presence of cardiac problems
- ❑Hemodialysis in the presence of renal failure

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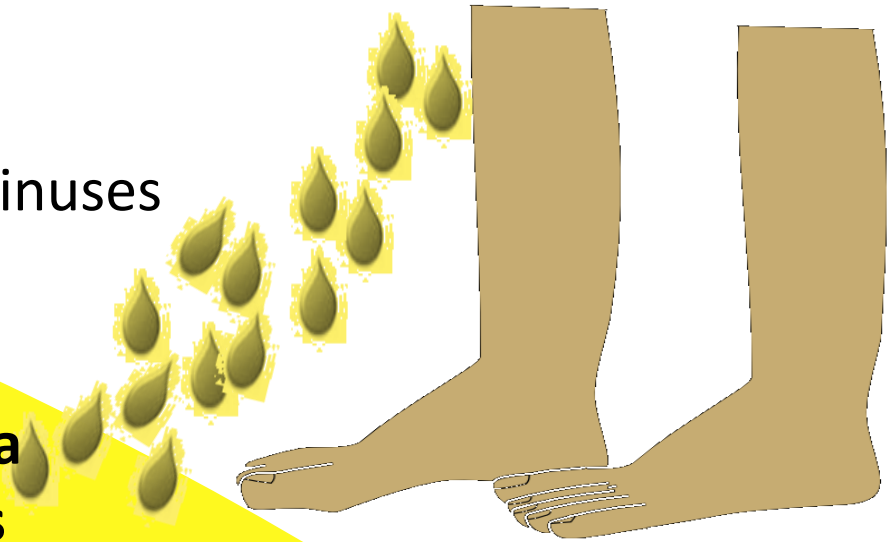
Hypophosphatemia Associated Cancer

❖Proximal tubular dysfunction: (Fanconi syndrome).

❖The syndrome of tumor-induced osteomalacia or oncogenic osteomalacia:

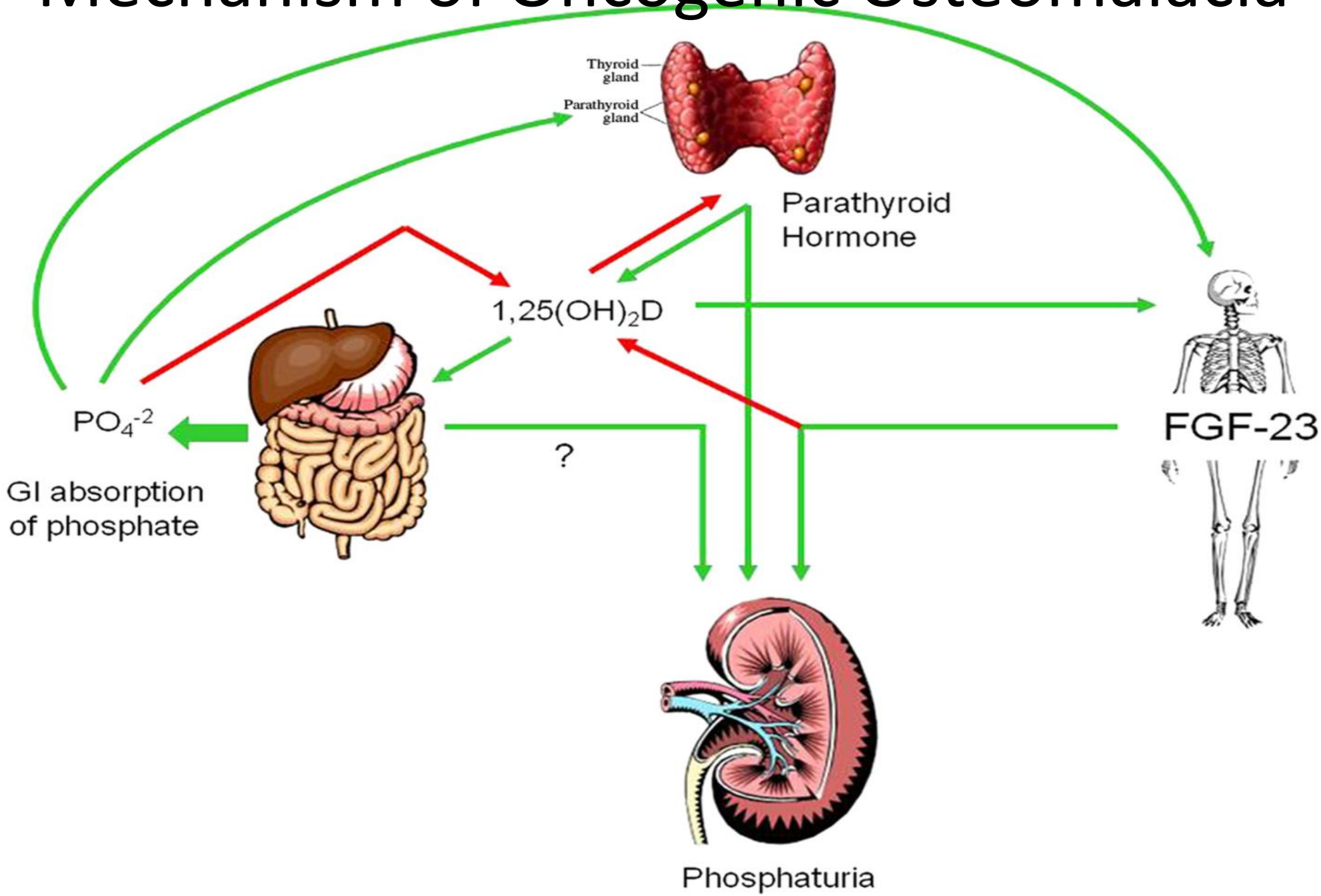
Tumor produces FGF-23 → chondrosarcoma, Osteoblastoma, Hemangiopericytoma → Renal phosphate wasting

Most neoplasms associated with TIO are found in the limbs or sinuses

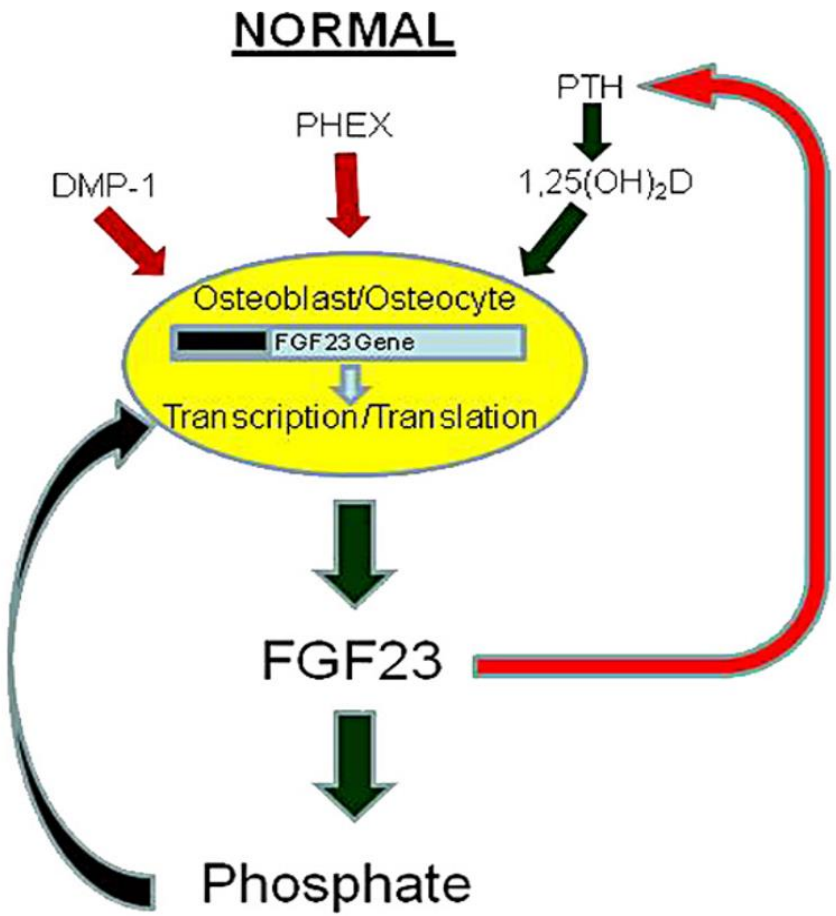


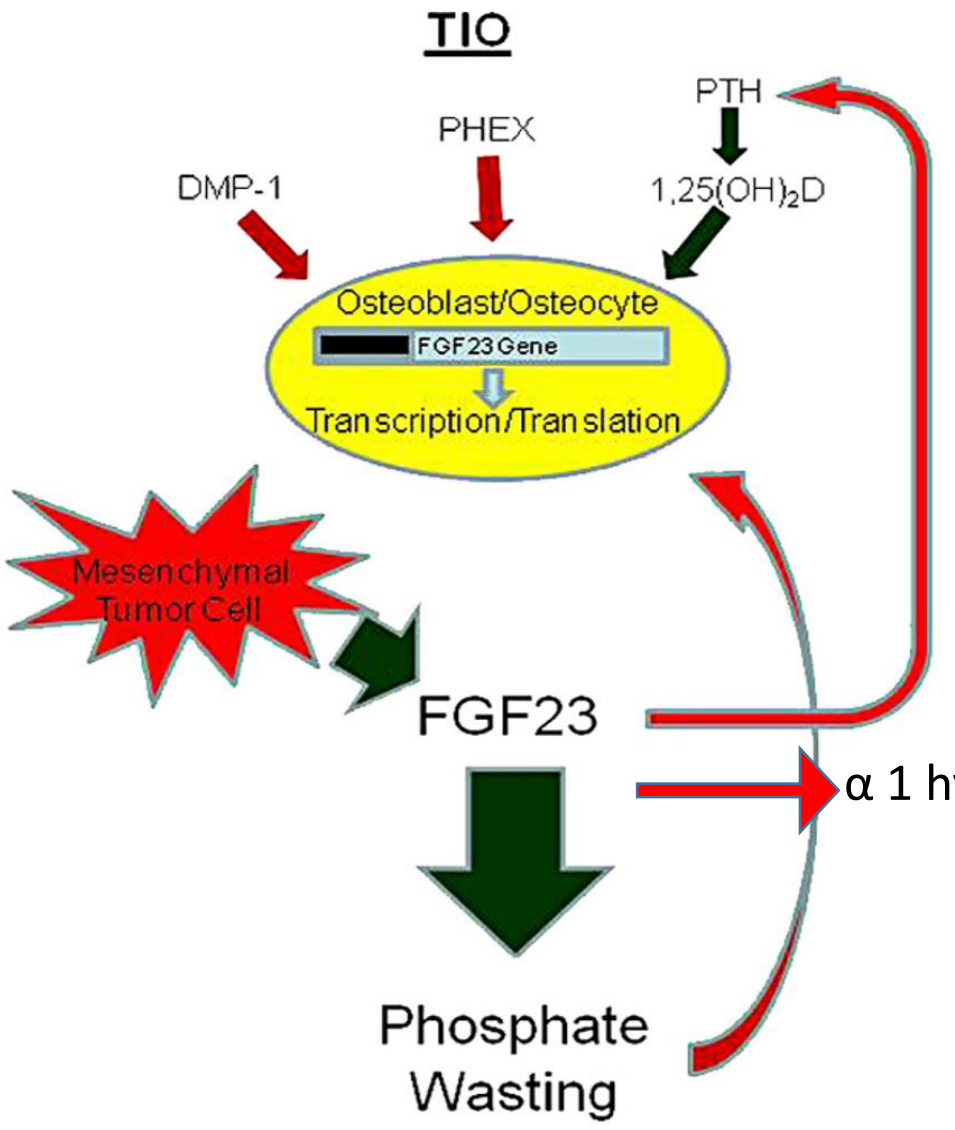
A fractional excretion of Po4 >5% in a hypo-phosphtemic patient indicates renal wasting of Po4

Mechanism of Oncogenic Osteomalacia



PET scan is a sensitive procedure for diagnosis.





α 1 hydroxylase antagonist

Vit D deficiency

Phosphate resistancy

The mainstay of therapy for this syndrome is tumor resection

Pseudo-hypophosphatemia should be excluded in patients containing paraproteins (MM).

Samples are analyzed after removal of serum proteins by ultrafiltration

Phosphorus Replacement Therapy

Product (Salt)	Phosphate Content	Initial Dosing Based on Serum K
Oral Therapy (Potassium Phosphate + Sodium Phosphate)		
Neutra-Phos® (7 mEq/ packet each of Na and K)	250 mg (8 mmol)/ packet	One packet three times daily[a]
Neutra-Phos-K® (14.25 mEq/packet of K)	250 mg (8 mmol)/ packet	Serum K >5.5 mEq/L (>5.5 mmol/L); not recommended
K-Phos Neutral® (13 mEq/ tablet Na and 1.1 mEq/ tablet K)	250 mg (8 mmol)/ tablet	Serum K >5.5 mEq/L (>5.5 mmol/L) one tablet three times daily
Uro-KP-Neutral® (10.9 mEq/tablet Na and 1.27 mEq/tablet K)	250 mg (8 mmol)/ tablet	Serum K >5.5 mEq/L (>5.5 mmol/L) one tablet three times daily
Fleets Phospho-soda® (sodium phosphate solution)	4 mmol/mL	Serum K >5.5 mEq/L (>5.5 mmol/L) 2 mL three times daily
IV Therapy		
Sodium PO_4 (4 mEq/mL Na)	3 mmol/mL	Serum K >3.5 mEq/L (>3.5 mmol/L) 15–30 mmol IVPB
Potassium PO_4 (4.4 mEq/ mL K)	3 mmol/mL	Serum K <3.5 mEq/L (<3.5 mmol/L) 15–30 mmol IVPB

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- **Hyperphosphatemia**
- Hypocalcemia
- Hypercalcemia

Hyperphosphatemia associated Malignancy

- TLS
- Hyper catabolic states associated AKI
- Pseudohyperphosphatemia: Multiple myeloma and Waldenström macroglobulinemia, circulating monoclonal proteins can interfere with the laboratory measurement of phosphate, resulting in spuriously elevated serum phosphate levels (pseudohyperphosphatemia).

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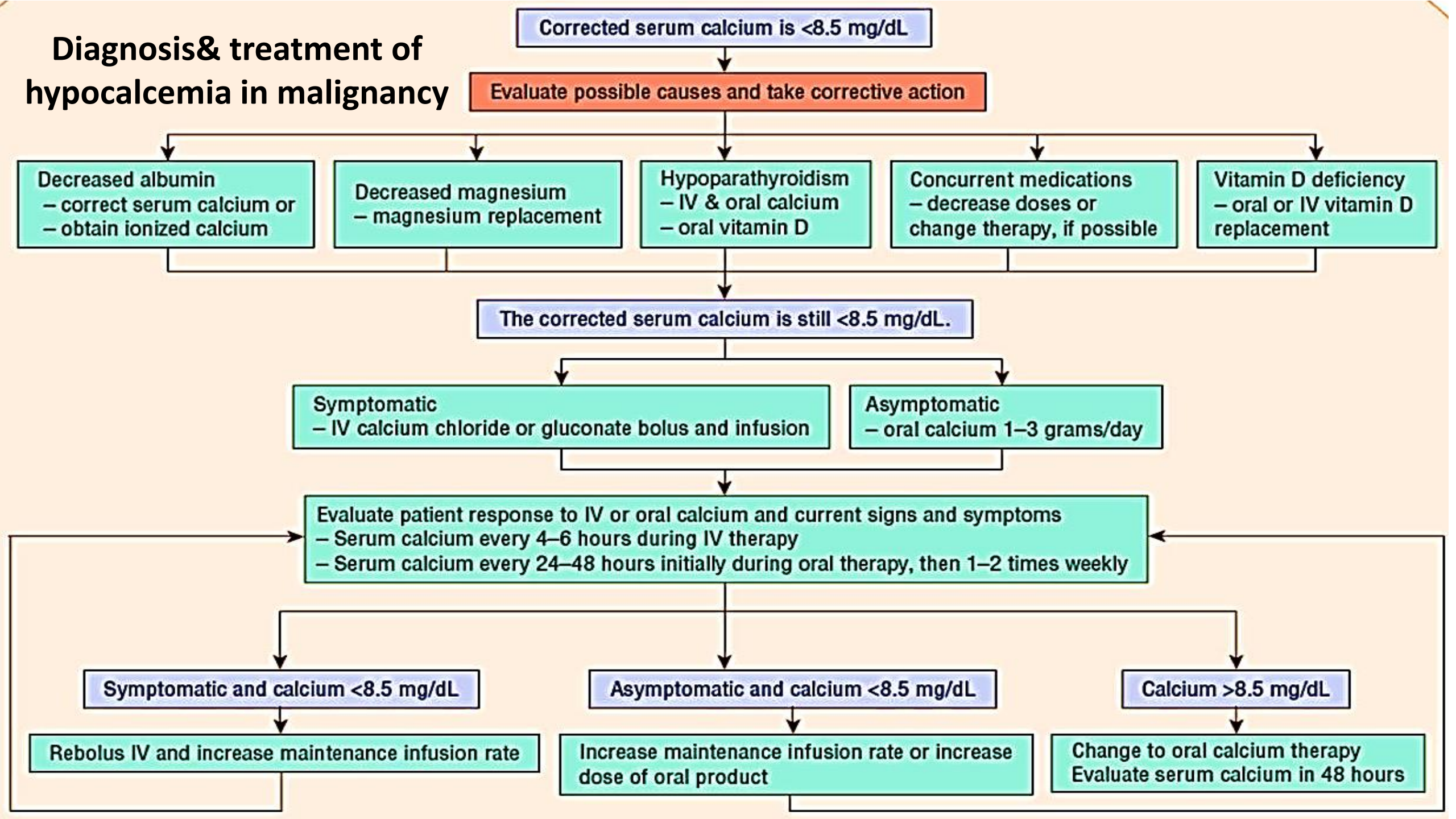
Malignancy induced Hypocalcemia

- Malignancies with Osteoblastic activity (prostate, and Breast)
- Metastatic malignancies to bone may find osteoblastic activity.
- Tumor lysis syndrome is an important cause of hypocalcemia.
- Hypocalcemia in the presence of malignancy should be suspicious for septicemia

Diagnosis& treatment of hypocalcemia in malignancy



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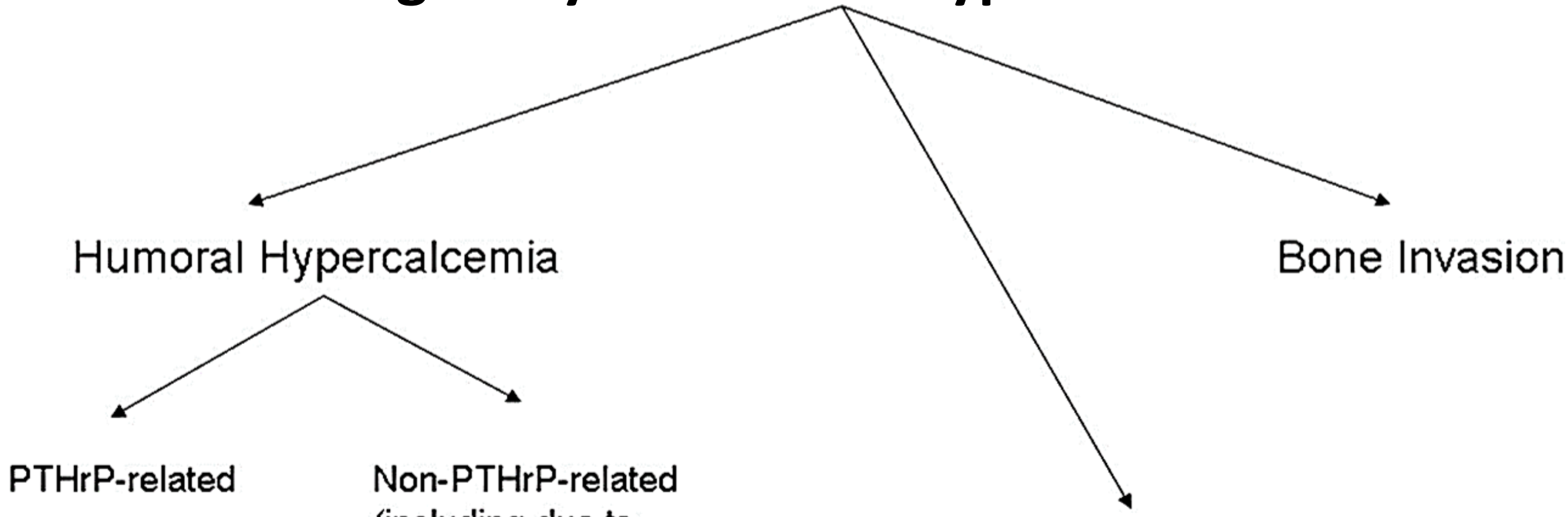
Malignancy-associated hypercalcemia



CJASN October 2012, 7 (10) 1722-1729

Malignancy induced Hypercalcemia

20%-30% of cancer patients experience hypercalcemia during the course of their malignancy and this is predictive of poor prognosis

The causes of Hypercalcemia	The types of Tumors
Release of PTHrP	Squamous-cell carcinomas of the lung, cervix, and esophagus Certain lymphomas Renal cell carcinoma Adenocarcinoma of the breast, prostate, and ovary
Release of PTH	Pulmonary, ovarian, thyroid, and pancreatic
❖ Direct metastatic tumor cells to cause local osteolysis ❖ By releasing factors such as prostaglandins or PTHrP.	Metastatic breast cancers Metastatic lung cancers Extensive multiple myeloma
Activation of vitamin D by the tumor itself	Hodgkin lymphoma and non-Hodgkin lymphoma. Multiple myeloma

Further Tests for Malignancy Induced Hypercalcemia

- Serum Phosphorus
- 1,25(OH)2D
- PTHrP
- Alkaline phosphatase
- Whole body scan
- Serum and urine protein electrophoresis looking for light-chain disease (An abnormal total serum calcium concentration in the presence of a normal ionized calcium concentration (**pseudohypercalcemia**) can occur in patients with multiple myeloma

Therapy of Malignancy induced Hypercalcemia

Depends on the mechanism by which hypercalcemia develops

To increase Calcium excretion

To decrease Calcium resorption

Short term

➔Aggressive intravenous hydration with 0.9% saline, usually at 200 to 500 mL/hour, is the initial regimen suggested to establish a kidney urine output of more than 75 mL/hour➔ addition of furosemide If hydration results in excessive fluid retention and potentially cardiac compromise➔ Furosemide dosage is increased only after vigorous hydration has been achieved

Long-term➔

(1) Anti-resorptive drugs: RANKL inhibitor: Denosumab

➔Bisphosphonates include: Pamidronate, Zolendronic acid, and Ibandronate

(2) Anti 1 alpha Hydroxylase: Hydrocortisone 200-300 mg/d for 5 days ➔ reduce to oral prednisolone 10-30mg/D

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Caused by Anti-cancer treatment

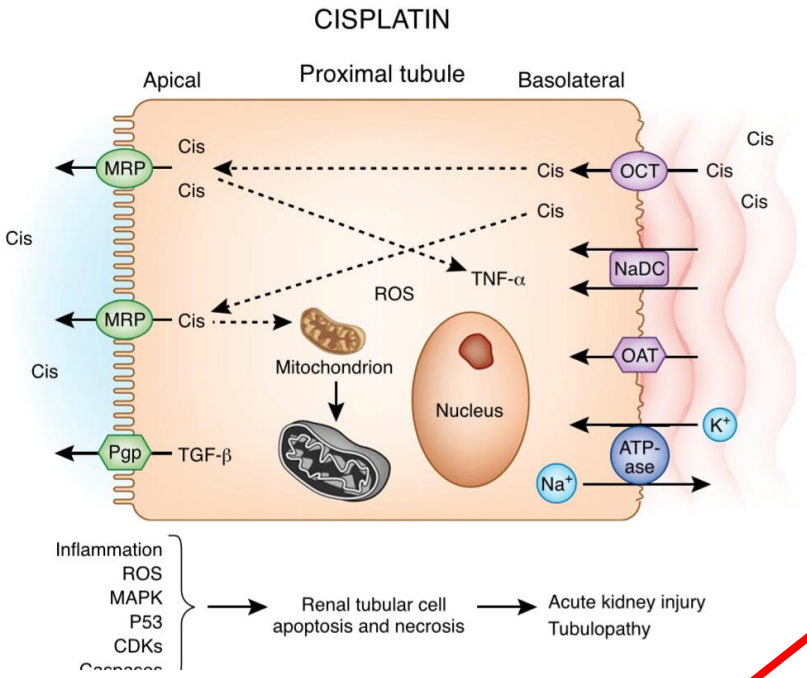
Anticancer drugs, type of nephrotoxicity, mechanism and prevention of renal adverse events

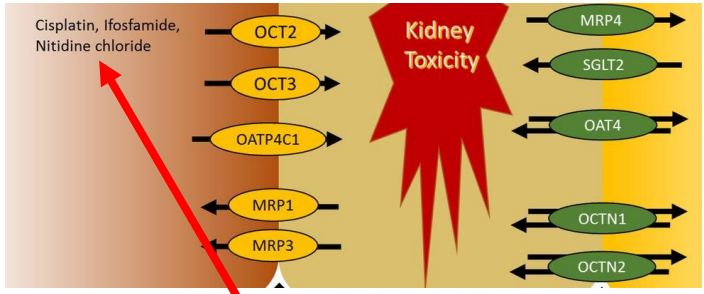
Medication	Nephrotoxicity	Mechanism of action	Preventive measures
Alkylating agents	Hyponatraemia-SIADH	Direct effect on distal tubules	Adequate hydration
cyclophosphamide	haemorrhagic cystitis	proximal tubular damage by acrolein and chloroacetaldehyde	use of Mesna or N-acetylcysteine
ifosphamide	Fanconi syndrome, renal tubular acidosis, nephrogenic diabetes insipidus		electrolyte monitoring
Antitumour antibiotics Mitomycin C	DITMA	Direct endothelial injury	Drug discontinuation, supportive care
Antimetabolites	AKI non-oliguric (high dose)	Precipitation of methotrexate and its crystals	Adequate hydration urine alkalinization, forced diuresis
methotrexate	Hyponatraemia-SIADH		
pemetrexed gemcitabine	AKI, acute tubular necrosis, renal tubular acidosis, diabetes insipidus	Decrease in GFR due to arteriolar or mesangial cell constriction	Drug discontinuation, supportive care
clofarabine	DITMA AKI		
Thalidomide and derivatives	AKI, Interstitial nephritis	Crystal nephropathy	Adequate hydration
Vinca alkaloids	Hyponatraemia DITMA	SIADH	
Platinum derivatives	Renal failure, renal tubular acidosis, hypomagnesaemia (dose-related and cumulative) Recurrent salt wasting	Tubular injury	Aggressive hydration Forced diuresis
Proteasome inhibitors	Thrombotic microangiopathy AKI		Drug discontinuation, supportive care
Anti-angiogenesis drugs	Proteinuria, nephrotic syndrome Hypertension	Anti-VEGF antibodies	
VEGF pathway inhibitors, TKI	AKI, thrombotic microangiopathy		
EGFR pathway inhibitors	Hypomagnesaemia	Tubular injury	
BRAF inhibitors	AKI, acute interstitial nephritis acute tubular necrosis, Fanconi syndrome, electrolyte disturbances SIADH	Tubular toxicity	
ALK inhibitors	AKI		Supportive care
Checkpoint inhibitors	Acute interstitial nephritis	Suppression of T-cell immunity cell-mediated immunity, potential autoimmune mechanism	
Anti-PD-1 and PDL-1 therapies Anti-CTLA-4 antibody	Acute interstitial nephritis, AKI, acute tubular necrosis, acute tubular injury, nephrotic syndrome		
Interleukin-2	AKI	Capillary leak syndrome leading to prerenal AKI	Control volume and haemodynamic status Avoid other nephrotoxins
Rituximab	AKI, electrolyte disturbances	Tumour lysis syndrome	
Interferons	Proteinuria, nephrotic syndrome Thrombotic microangiopathy	Minimal changes	

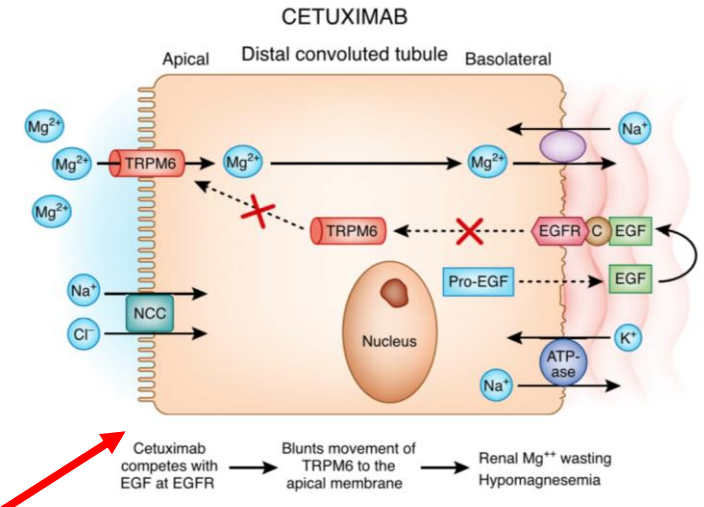
Alkylating agents (cyclophosphamide, Ifosfamide)

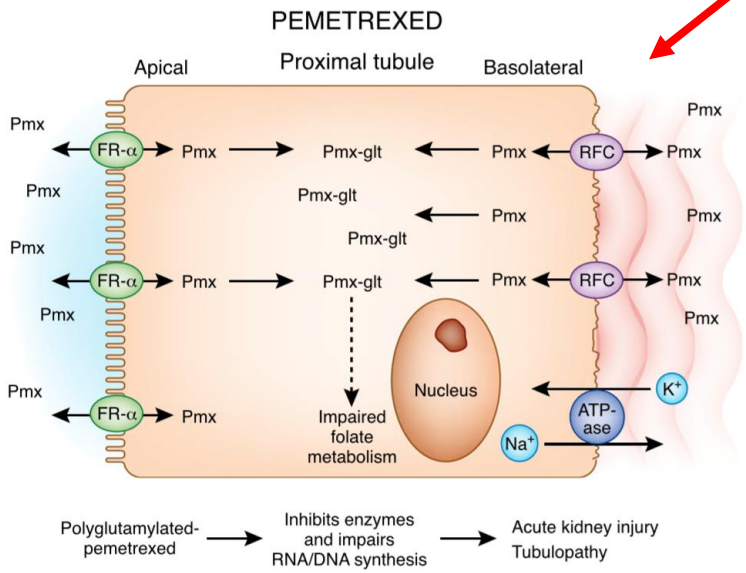
- Cause the SIADH, similarly to melphalan. (occurs acutely and resolves within 24 hours after discontinuation of the drug).

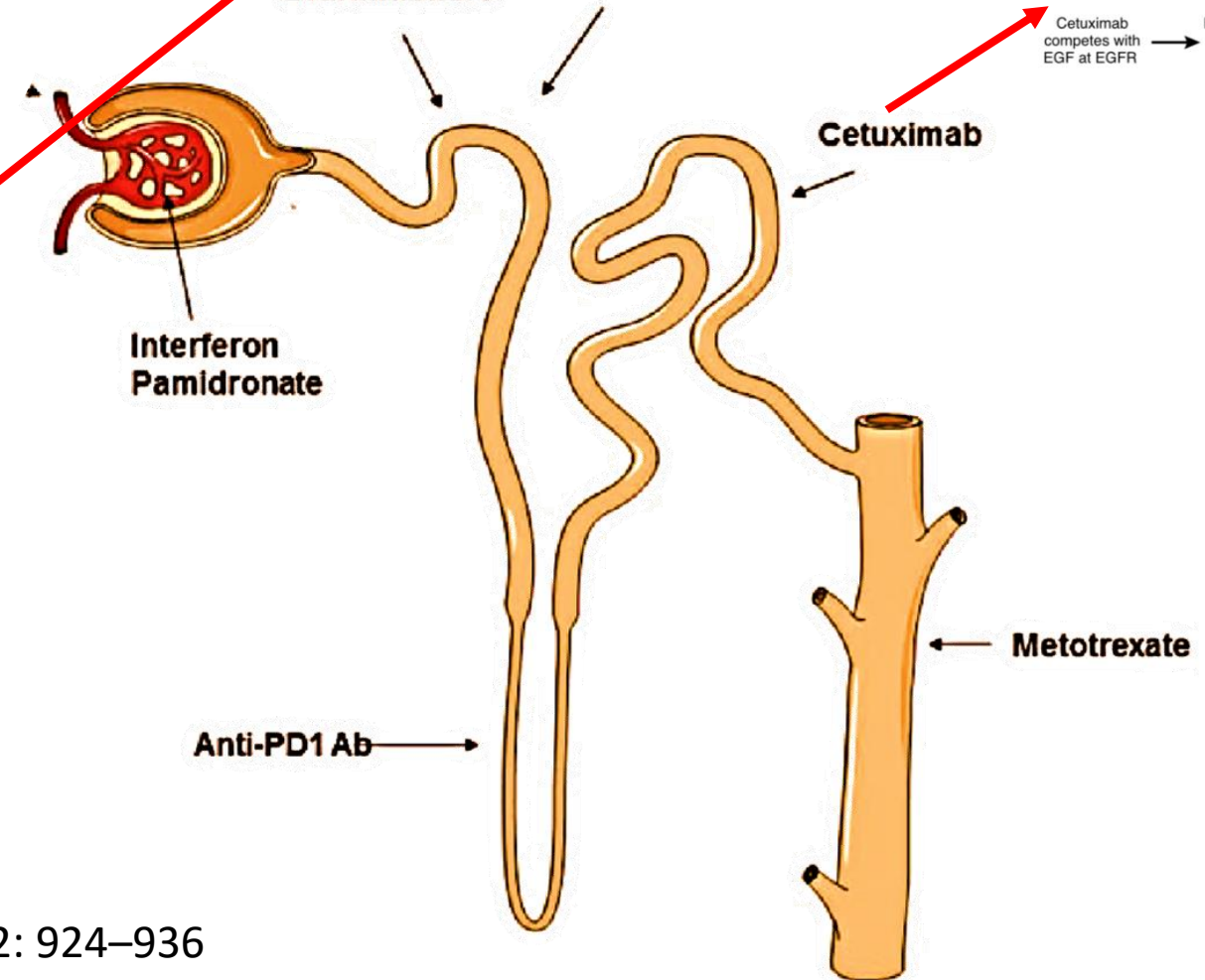
- Ifosfamide nephrotoxicity could be manifested as an type 1 & type 2 RTA with fanconi syndrome.





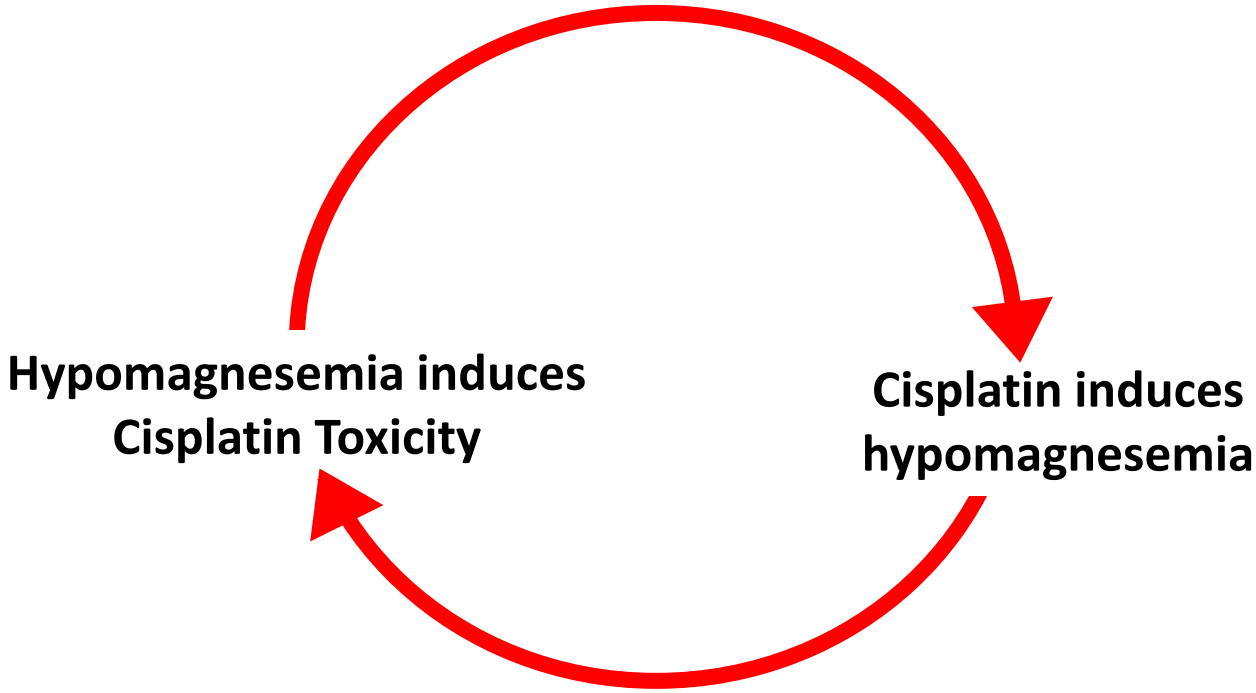






Nephrol Dial Transplant (2017) 32: 924–936

Hypomagnesaemia in Cisplatin is due to urinary magnesium wasting



Cisplatin nephrotoxicity may be enhanced by the concomitant presence of hypomagnesemia

→ IV Mg therapy on the day of cisplatin administration → and 2–3 days after therapy.

J Nephropharmacol. 2018; 7(2): 126–130.

http://www.jnephropharmacology.com

Journal of Nephropharmacology

doi: 10.15171/npj.2018.04

Frequency of electrolyte imbalance associated with cisplatin in oral cancer patients; a tertiary care experience from Pakistan

Kashif Gulzar*, **Maseer Ahmed, Abdul Manan Junejo**

Nephrology Unit, Jinnah Postgraduate Medical College, Karachi, Pakistan

Serum electrolyte	Pre-cisplatin	Post-cisplatin	Decrease in electrolytes	*P* value
P (mEq/dL) (n = 90)	4.02±0.30	3.13±0.31	0.63±0.15	0.002
Ca (mg/dL) (n = 87)	9.12±0.46	8.02±0.32	0.76±0.32	0.03
Mg (mg/dL) (n = 66)	2.26±0.34	1.39±0.28	0.45±0.12	0.003
Na (mEq/dL) (n = 66)	141.6±4.9	130.2±3.1	5.82±1.06	0.6

Conclusion

- Electrolyte abnormalities occur frequently in the cancer patient and contribute to poor quality of life.
- Disturbances in electrolyte may occur due to the cancer itself or due to adverse effects of therapy.
- Treatment of electrolyte disorders in cancer should be etiology specific and patient centered
- Until the electrolyte abnormalities are corrected, efficacy of anti cancer therapy might not be fully achieved

THANK YOU

for your

ATTENTION!